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Neurologic Abnormalities in the Skeletal Dysplasias: A Clinical and Radiological Perspective

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The neurologic manifestations of the skeletal dysplasias are reviewed. Three important major groups are identified: *Achondroplasia* (cranio-cervical junction problems in infancy, spinal stenosis and neurogenic claudication in the adult). *Type II collagenopathies* (upper cervical spine anatomic and functional problems), and *craniotubular and sclerosing bone dysplasias* (osseous overgrowth with foraminal obstruction problems). The remainder of the well-identified 150 or so bone dysplasias are also evaluated in depth for their diverse neurologic abnormalities. The findings discussed are important both for the diagnosis and management of these patients. Am. J. Med. Genet. 69:33–43, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: skeletal dysplasias; bone dysplasias; osteochondrodysplasias; neurologic abnormalities

INTRODUCTION

The most important neurological abnormalities in the skeletal dysplasias are the central nervous system (CNS) and high cervico-medullary problems in *achondroplasia* and the upper cervical spine complications in the *Type II collagenopathies* and their related disorders. However, a large variety of neurological associations and manifestations may occur in many of the 150 or so well-defined skeletal dysplasias. They are important not only for diagnostic purposes, but also at times for clinical management.

ACHONDROPLASIA

Achondroplasia is due to a defect in enchondral bone formation with resulting decrease in growth, not only of long bones but also a decrease in size of the vertebral bodies and of the diameter of the posterior vertebral arches. The foramen magnum is also affected with resultant decrease in its size and alterations in its shape, especially at the expense of its lateral walls. Secondarily, there is a potential for over growth of membranous bone (the greatest portion of the skull convexity).

The early life (infancy) neurologic complications of achondroplasia are found at the cranio-cervical junction and relate to the "small foramen magnum"—an oxymoron. Secondary *significant hydrocephalus* may occur but is infrequent, it is communicating, associated with intracranial venous hypertension, megalencephaly and medullary, and upper cervical cord compression. The cranio-cervical compression can exist independent of the hydrocephalus and may manifest as sleep apnea and "aborted" or "real" Sudden Infant Death "syndrome," apneaustic breathing [Mador et al., 1990], and increasing upper limb weakness. A recent study suggests that the best predictors of the need for suboccipital decompression include the demonstration of lower limb hyperreflexia (or clonus); central hypopnea (apnea) at poly-somnography; and reduced foramen magnum measurements [Pauli et al., 1995].

Radiographic evaluation should include: (1) CT of the foramen magnum (size) and brain (hydrocephalus), and (2) MRI of the brain and upper cervical-medullary region, including CSF flow studies across the foramen. MRI performed in the flexed neck position may also contribute important information.

Other abnormalities detected on imaging include: upper cervical cord thinning secondary to compression and cord syrinx following infarction/hemorrhage (Figs. 1–5).

Recently, a nontraumatic cervical cord infarction in a 12-year-old with resultant quadriplegia has been reported [Wieting and Krach, 1994]. It is apparent that the achondroplastic patient is "not out of the woods" for this complication even in later life.

Usually later in life (young/late adult), nerve root compression (spinal stenosis) occurs as well as inter-

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The author submits this manuscript in honor of the 65th birthday of Jürgen Spranger, colleague, pioneer, discerning spirit, but most of all—a good friend. I wish him many more wonderful years with us among the skeletal dysplasias.

Wenn man einen Zwerg gesehen hat, hat man alle gesehen (if you have seen one dwarf, you've seen them all). He as much as anyone has shown us the absolute *untruth* in that statement.

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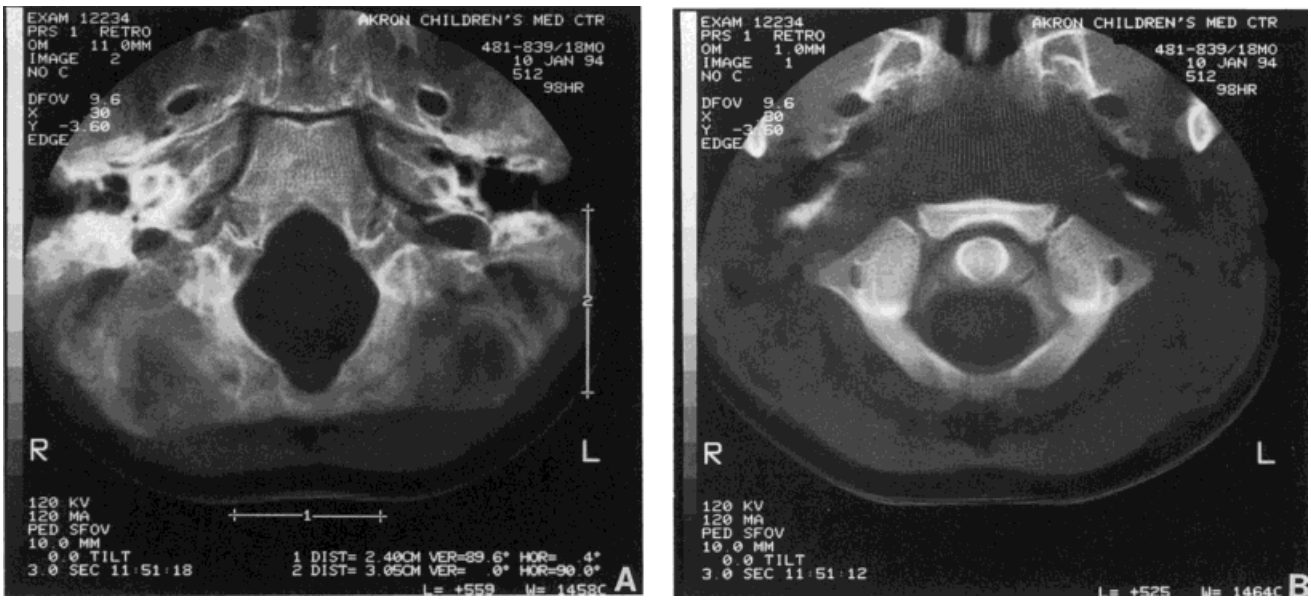

Fig. 1. Six-month-old achondroplasia patient. **A, B**: CT of the skull revealing decreased side wall diameter of the foramen magnum and oval shape to the foramen magnum. In contrast, there is a normal C_1C_2 diameter and shape at the odontoid level.

mittent (or persistent) neuron claudication, most commonly in the lumbar spine resulting in parasthesias and progressive paraparesis and even rarely quadriparesis [Fortuna et al., 1989].

Imaging of these problems includes: (1) plain films (AP and lateral) of the spine, and (2) MRI of spine area in question. Imaging findings may include: (1) spinal stenosis, (2) hypoplastic T12/L1 vertebral body, (3) herniated discs (multiple sites), and (4) nerve entrapment.

The *clinical situation* must be evaluated as well as the imaging studies to decide if laminectomy should be performed. Postlaminectomy recurrences are not rare. Two much rarer neurologic entities described in achondroplasia are tethered cord [Phadke et al., 1990], and brain tumor [1 case] [McArdle et al., 1984].

TYPE II COLLAGENOPATHIES

Most of the type II collagenopathies manifest abnormalities in the cervical spine (Table I). These abnor-

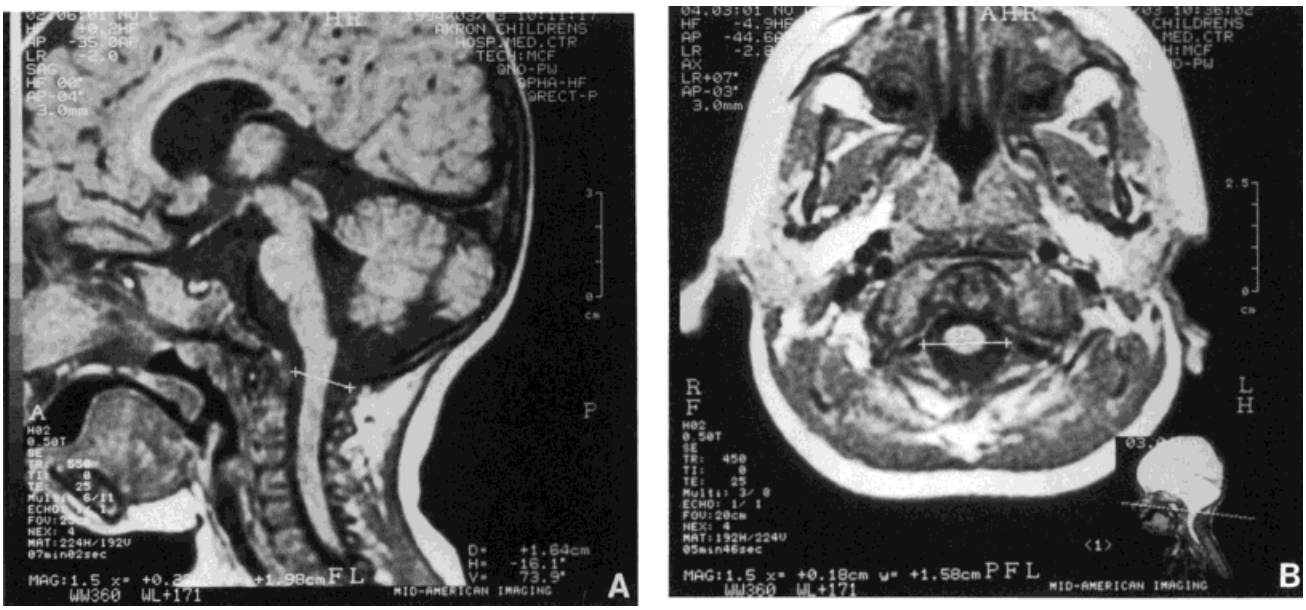

Fig. 2. Same patient as Figure 1. **A, B**: MRI of the brain stem and cervical spine with measurements of both anterior-posterior and lateral dimensions of the foramen magnum. There is no evidence of cervical cord compression.

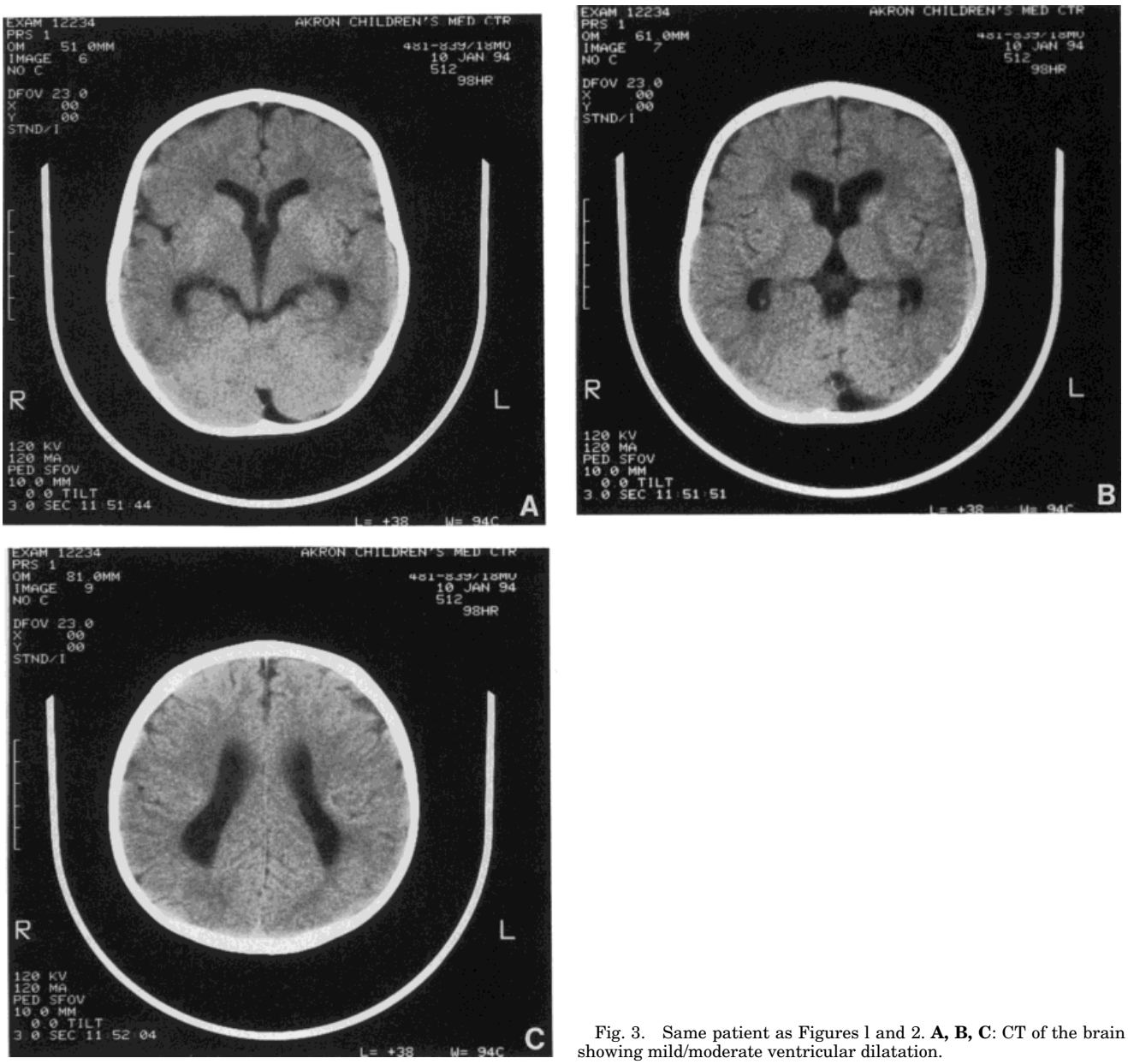

Fig. 3. Same patient as Figures l and 2. **A, B, C**: CT of the brain showing mild/moderate ventricular dilatation.

malities include C1-C2 subluxation/dislocation secondary to abnormal formation of the odontoid process, the base of C2, ossification of C1, and abnormally lax or non-fixed posterior portion of the ligament extending from C1 to C2. Any or all of the abnormalities can result in the abnormal posterior displacement of C2 into the neural canal, especially with extreme flexion. Clinically, this problem can manifest throughout life, but even in infancy it may occur especially if the patient needs intubation (i.e., for anesthesia) or suffers trauma and the neck is acutely flexed. All patients with a type II collagenopathy, except for Stickler dysplasia, should be screened for this problem and patients with unclassifiable forms of SED [Anderson et al., 1982; LeDoux et al., 1991; Merrill et al., 1989; Yagi et al., 1987].

Imaging studies should include: (1) AP and lateral cervical spine (2) lateral flexion/extension views of the cervical spine, (3) CT (with/without) reconstruction of the C-spine for anatomic delineation, if necessary, and (4) MRI of the cervical cord region for possible cord damage. One should note that the most important studies for evaluation are 2 and 4 (Figs. 6–8).

Recently, doubt has been raised about the frequency of this problem in patients with some forms of SED (SEMD), which has not been the experience of most [Reardon et al., 1994]. Our experience suggests that those with a pectus carinatum (high sternum) are protected by the inability to flex significantly.

As one goes through the remainder of the 150 well-defined skeletal dysplasias, it is apparent that there is

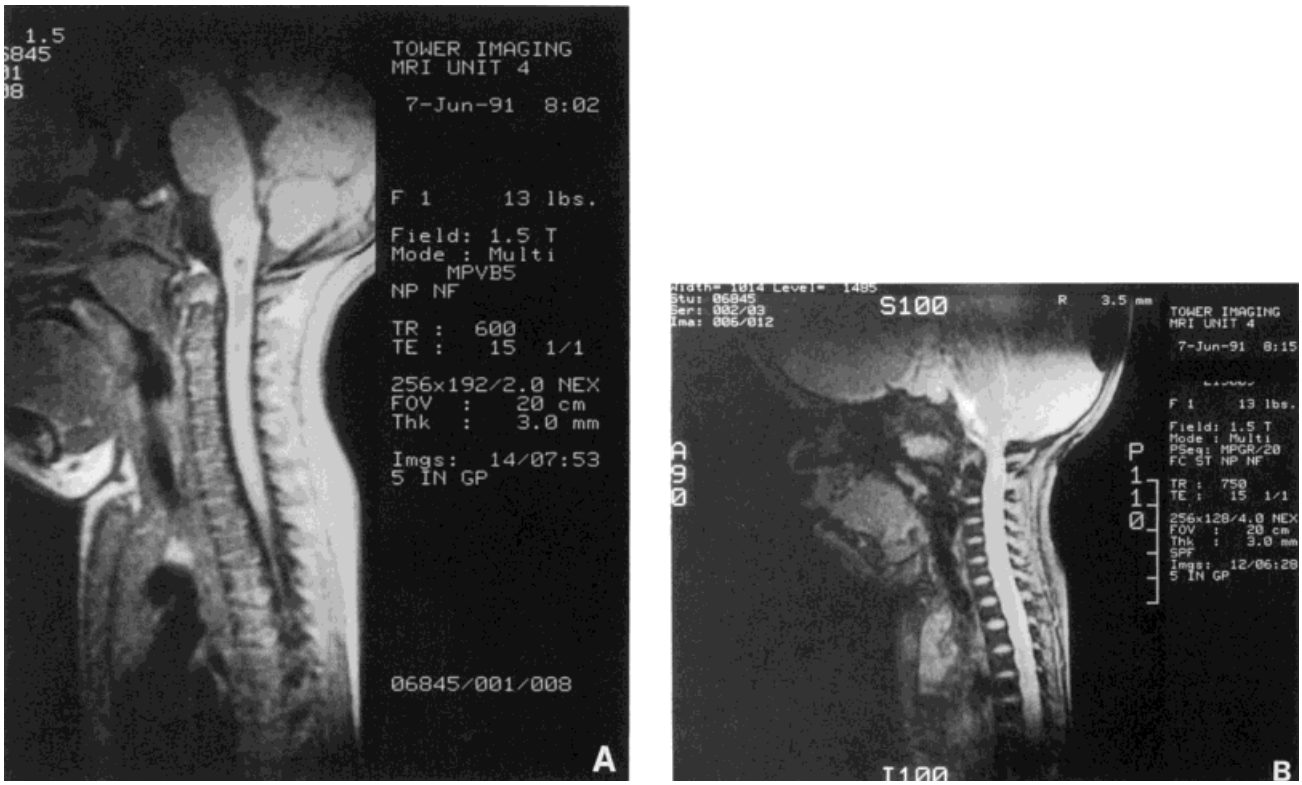

Fig. 4. Four-month-old infant with achondroplasia. **A, B**: MRI of the cervical cord and brainstem (preoperatively) with a syrinx of the cervical cord and cervical cord compression at the medullary-cord junction.

a large variety of other neurologic abnormalities, associations, and complications. Many of these are related to the skeletal changes themselves. The less important ones are covered in Table II.

CAMPOMELIC DYSPLASIA

This entity may or may not be lethal and commonly has mild or severe CNS abnormalities, which can present with generalized hypotonia. Severe cervical kyphosis may lead to cervical cord problems [Coscia et al., 1989].

Chondrodysplasia Punctata (CP) Group of Disorders

CP—Rhizomelic type. This peroxisomal enzyme abnormality disorder often results in perinatal or early infancy death. Survivors may manifest: facial paralysis, spastic quadriplegia, generalized spasticity, and severe psychomotor retardation [Lenti et al., 1991, Williams et al., 1991]. They appear to be in chronic pain [Rimoin, 1996].

CP—Conradi-Hunermann type. Four cases of progressive myelopathy have been described [Goodman et al., 1990].

CP—Brachytelephalangic type. Hypotonia has been a prominent symptom and sign (Fig. 9).

Cranio-Tubular Dysplasias and Sclerosing Bone Dysplasias

In several of these dysplasias, there is osseous overgrowth of the skull base and encroachment of the foramina resulting in neurologic and neurovascular problems [Kirkpatrick et al., 1977].

Craniodiaphyseal dysplasia. Increasing deafness, vision loss and sudden death, probably on a vascular basis.

Craniometaphyseal dysplasia. Hydrocephalus, optic atrophy, progressive deafness, facial nerve palsy, hemiplegia, quadraplegia, and medullary compression have been noted [Allen et al., 1982; Hudgins et al., 1987; Saper et al., 1974].

Diaphyseal dysplasia, Engelmann type. Increased intracranial pressure (hydrocephalus), progressive hearing loss, and visual loss may occur [Applegate et al., 1991; Paludetti et al.; 1994].

Dysosteosclerosis. Beginning in adolescence, decreased visual acuity, optic atrophy, and facial palsy [Chitayat et al., 1992]. These findings are not seen in the dominant form of osteopetrosis.

Endosteal hyperostosis, Van Buchem. Hydrocephalus (increased intracranial pressure) and rarely spinal cord compression may occur. Cranial nerve palsies, especially of the facial nerves, are not infrequent [Fryns et al., 1988; Kitasawa et al., 1986].

Fig. 5. Same patient as in Figure 4, 2 months later. The postoperative MRI study shows the surgically induced posterior ossification defects producing increased space for the cord.

Endosteal hyperostosis, Worth. Mild facial, optic, and auditory nerve involvement may occur with progression in the adult (5 cases). Chronic increased intracranial pressure and cerebellar tonsillar henation into the foramen magnum were reported recently [Adès et al., 1994].

Frontometaphyseal dysplasia. Progressive hearing loss has occurred in a few patients [Arenberg et al., 1974].

Osteopathia striata with cranial sclerosis. Facial nerve palsy can be seen as well as other mild cranial nerve abnormalities such as deafness and ophthalmoplegia [Gay et al., 1994].

TABLE I. Type II Collagenopathies

Name	Cervical spine problems
Achondrogenesis II	Lethal
Hypochondrogenesis	Yes
Spondylo-epiphyseal dysplasia (SED) congenita	Yes
Spondylo-epi-metaphyseal dysplasia (SEMD) Strudwick	Yes
Kniest dysplasia	Yes
Stickler dysplasia[a]	No
Autosomal dominant spondyloarthropathy (mild SED)	?
Goldblatt syndrome (SEMD with dentinogenesis imperfecta and joint laxity)	?
SED-Namaqualand	?
SED-Capetown	?

[a] Cervical myelopathy secondary to spinal stenosis (Noel).

Osteopetrosis. The severe autosomal *recessive* form can manifest with multiple cranial nerve palsies, including facial, optic and auditory involvement in infancy [Abdel-al et al., 1994; Al-Mefty et al., 1988; Bartgaski et al., 1989; Benecke et al., 1993; Demirci et al., 1991; Elster et al., 1992; Wilms et al., 1990]. Myelopathy secondary to cervical spine involvement can occur [McCleary et al., 1987].

The autosomal *dominant* form has presented with carpal tunnel syndrome [Rakic et al., 1986].

Sclerosteosis. Cranial nerve palsies especially involving the seventh nerve can be seen as well as

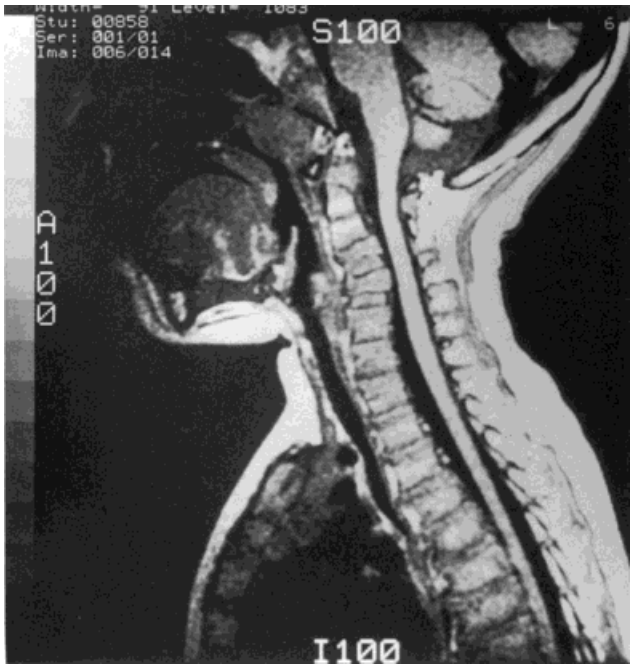

Fig. 6. Three-year-old with spondyloepiphyseal dysplasia (SED) congenita. The MRI of the cervical region reveals C_3, C_4, C_5 posterior subluxation with cord compression in the neutral position.

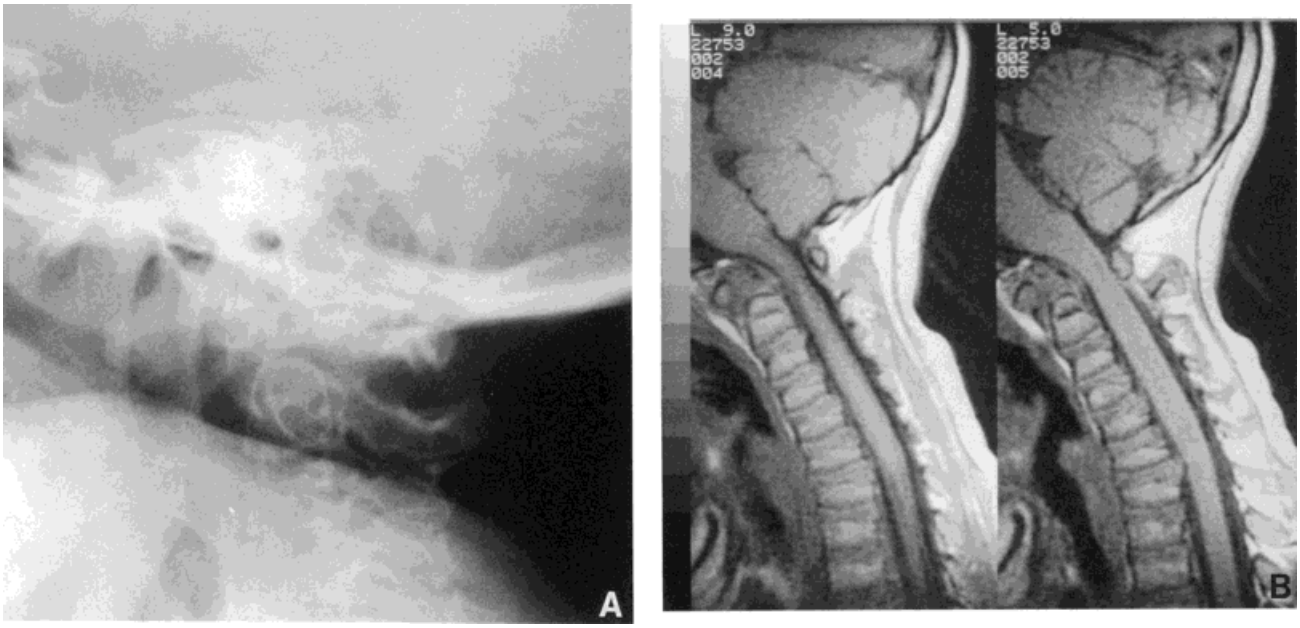

Fig. 7. Seven-year-old with SED congenita. **A, B:** MRI shows typical C_1C_2 subluxation with cord impingement.

increased intracranial pressure (hydrocephalus) [Dort et al., 1990; duPlessis et al; 1993; Hill et al., 1986].

DIASTROPHIC DYSPLASIA

There is significant cervical kyphosis in about ⅓ of patients, with resultant cervical cord compression in some. Quadriplegia may occur especially related to anesthesia [Krecak et al., 1987; Lachman et al., 1981; Richards et al., 1991].

DYGGVE-MELCHIOR-CLAUSSEN DYSPLASIA

The more severely involved cases may exhibit progressive basilar impression and even brain death [Spranger et al., 1976].

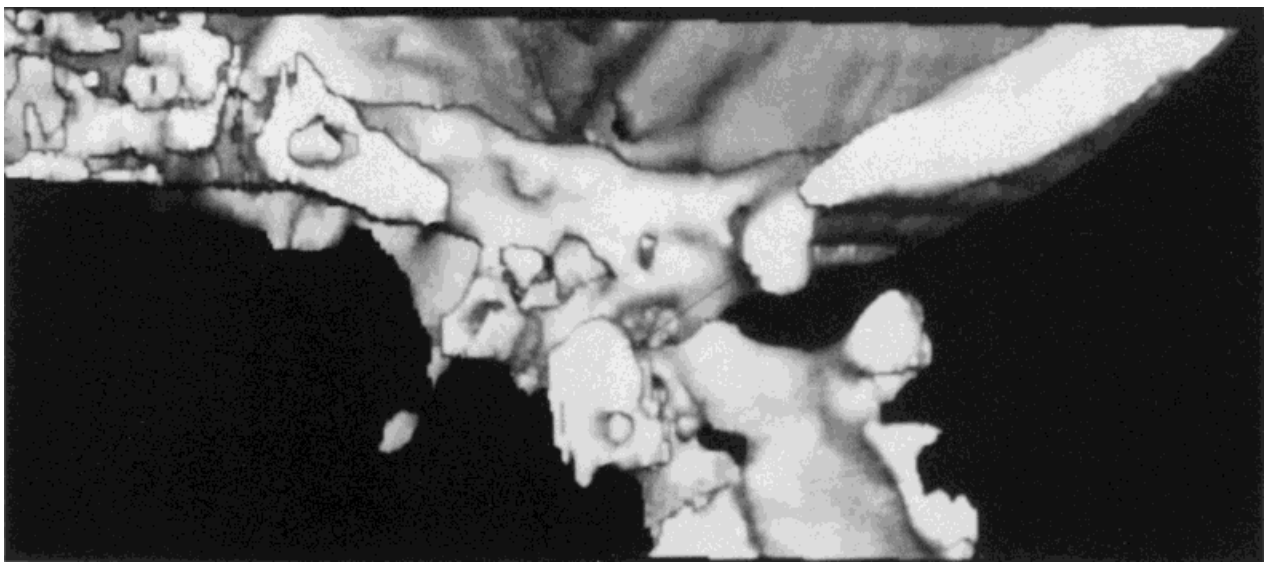

Fig. 8. Same patient as in Figure 7. CT reconstruction reveals the odontoid hypoplasia with an Os odontoideum. The measurement of the anterior-posterior cervical spine dimension and posterior dislocation of C_2 is apparent.

TABLE II. Other Skeletal Dysplasias With Neurologic Abnormalities

Skeletal dysplasia	Abnormality	Frequency	References
Acrodysostosis	Psychomotor retardation	77% of cases	Taybi, Lachman, 1996
	Lower extremity neuropathy (lumbar stenosis, tight dural sac)	Uncommon	Hamanshi, 1993
	Optic atrophy, strabismus, seizures and choreoathetosis	Rare	
Acrodysplasia with retinitis pigmentosa and nephropathy (Saldino-Mainzer dysplasia)	Tapetoretinal degeneration	Major manifestation	Ellis, 1984
	cerebellar ataxia	Uncommon	Popovic-Rolovic, 1976
Acromesomelic dysplasia	Syrinx of the cervical cord	2 cases	personal experience
	Hydrocephalus	Rare	
Asphyxiating thoracic dysplasia	Agenesis of the corpus callosum	Uncommon	Trabelsii, 1990
	Dandy Walker malformation		
Atelosteogenesis type I	Forebrain abnormalities with encephalocele	Frequent	Chervenak, 1986
Boomerang dysplasia	Encephalocele	?	Canki-Klain, 1992
Cleidocranial dysplasia	Syringomyelia	3 cases	Dore, 1987
Desbuquois dysplasia	Sleep apnea and sudden infant death syndrome (SIDS) with cervical kyphosis	Several cases	Sillence, 1995 Beemer, 1994
Dyssegmental dysplasia-			
Rolland-Desbuquois type	Hydrocephalus	Common	Aleck, 1987
Silverman-Handmaker type	Dandy Walker cyst	Common	
Lowry Wood dysplasia (MED, Lowry-Wood)	Hypoplasia of corpus callosum	1 case	Yamamoto, 1995
Metaphyseal chondrodysplasia, Swachman-Diamond type	Focal pontine leudodystrophy	3 cases	Andres, 1993 Mah, 1987 Steinsapir, 1985
Metaphyseal-Sella turcica dysplasia (Rosenberg)	Thickening of sella turcica without clinical symptomatology	?	Rosenberg, 1986
Multiple exostosis	Pain, parasthesias, and motor problems secondary to exophytopic impingement	Common	N'dri, 1994 O'Brien, 1994
Opsismodysplasia (Fig. 10)	Hyptonia, C1C2 dislocation and cord compression with severe ossification defect	Common	Zonana, 1977
Osebold Remondini dysplasia	Numbness and dysthesias (pathogenesis unclear)	?	Taybi, Lachman, 1996
Osteopoikilosis	Lumbar spine stenosis with clinical symptomatology	?	Weisz, 1982
Pseudodiastrophic dysplasia	Hydrocephalus	1 case	Taybi, Lachman, 1996
Pycnodysostosis	Sleep apnea (medullary compression-bony overgrowth)	?	Floman, 1989
	Hangman fractures (spondylolysis of cervical spine)	Uncommon	Currarino, 1989
	Porencephalic cyst	1 case	Figueiredo, 1989
Short rib polydactyly dysplasia Type II and IV	Severe brain abnormalities (arrhinencephaly, vermis hypoplasia, arachnoid cysts and cerebral dysgenesis)	Common	Pradio, 1993
Type IV	Optic atrophy (chiasm and nerves)	?	Cideciyan, 1993
Spondylometaphyseal dysplasias (SMD)			Taybi, Lachman, 1996
SMD-corner fracture (Schmidt-Sutcliffe) type	C_1C_2 subluxation	1 case	
SMD-Sedeghation type	Lissencephaly	?	
SMD-Frydman type	Quadriparesis and basal ganglia calcifications	?	
Tricho-rhino phalangeal dysplasia, type I	Mental retardation and seizure disorder	Very common	Hamers, 1985 Balza, 1990
Weissenbacher-Zweymuller dysplasia	Neural tube defect	2 cases (Monozygotic twins)	Ramer, 1993
Walcott Rallison dysplasia (SED with Diabetes Mellitus)	Seizures, unrelated to hypoglycemia	1 case	Taybi, Lachman, 1996
Yunis Varon dysplasia	Agenesis of the corpus callosum	1 case	Taybi, Lachman, 1996

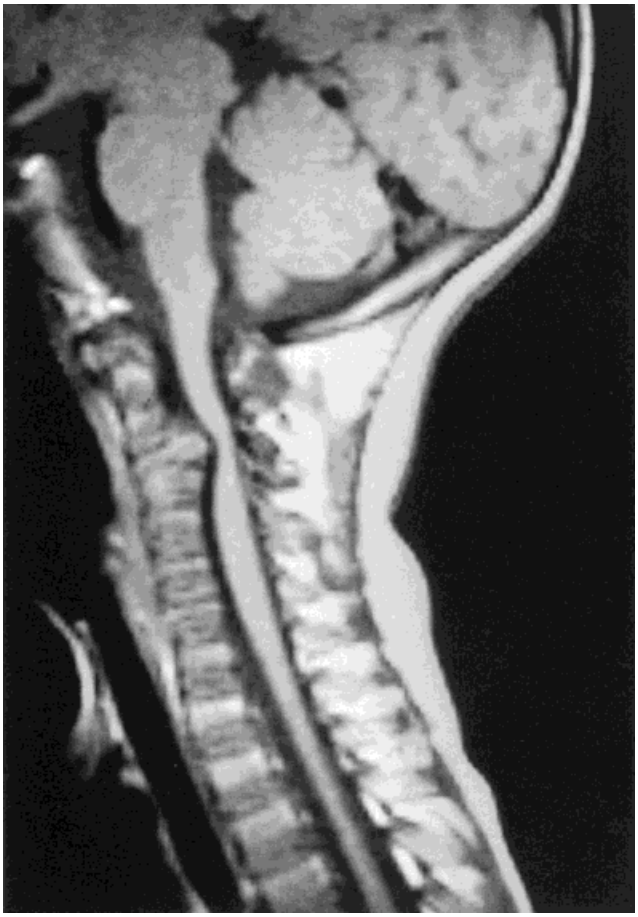

Fig. 9. Four-year-old with an unclassifiable form of chondropdysplasia punctata. An MRI of the cervical region shows cervical spine (C_3) subluxation with cord compression.

Fig. 10. Five-year-old with opsismodysplasia. On plain films of the cervical spine, one sees a severe lack of ossification of the cervical vertebral bodies in this rare disorder.

MAFFUCCI (SYNDROME) DYSPLASIA

This entity of multiple enchondromatosis and vascular abnormalities may have cranial nerve involvement when the base of the skull is affected. There have been five cases of brain tumors (gliomas) reported, a very high incidence for this rare entity [Nakayama et al., 1994; Robinson et al., 1994].

METATROPIC DYSPLASIA

Severe upper cervical spine problems are often present, especially C_1 C_2 subluxations/dislocations secondary to either hypoplastic or enlarged odontoid and/or a malformed base of C_2 resulting in sleep apnea and other symptoms similar to the type II collagenopathies. These patients definitely should be screened [Shohat et al., 1989]. Hydrocephalus also has been identified, as well as a recent report of a primary motor and sensory neuropathy with storage abnormalities in the rough endoplasmic reticulum of the nerve fibers similar to what is seen in the growth plate of bones [Yamashita et al., 1994].

OSTEOGENESIS IMPERFECTA (OI)

In the nonlethal OI type III, hydrocephalus with macrocrania is sometimes present [Charnas et al., 1993; Pauli et al., 1986; Rush et al., 1984; Tsipouras et al., 1986]. Recently, clinical manifestations secondary to basilar impression have been identified primarily in OI type IV [Sillence et al., 1994]. Rupture of a cerebral aneurysm in a fenestrated vertebral artery perhaps secondary to the underlying type I collagen defect also has been reported in OI type I (1 case). Reflex sympathetic dystrophy can occur [Karras et al., 1993].

THANATOPHORIC DYSPLASIA

This is probably the most common lethal skeletal dysplasia, with an incidence of almost 2 per 100,000 pregnancies. All cases with neuropathologic examination show severe brain abnormalities, including abnormal sulci with polymicrogyria and neuronal heterotopia and also marked hypoplasia of the middle and posterior cranial fossae. This suggests severe arrest of cerebral cortical development [Coulter et al., 1991]. Early extreme hydrocephalus with craniosynostosis is the pathogenesis in the group with Kleeblättschadel (cloverleaf skull). Rare survivors with thanatophoric dysplasia are all very severely neurologically impaired.

Mucopolysaccharidoses (MPS) and Mucolipidoses (ML)

In these groups, some exhibit significant neurologic manifestations, which depend on infiltrative deposition of MPS or oligosaccharide material into the brain, dura, or peripheral nervous system. Optic nerve infiltration can lead to blindness. One characteristic change in this group of disorders is the J-shape sella turcica produced

by the deposition of material (cystic in nature) within the cysternal spaces adjacent to the sella and eroding the bone without frank pituitary destruction [Nelson et al., 1988; Sheridan et al. 1994].

In addition, odontoid hypoplasia and C1 C2 subluxation as well as C3 C4 dislocations have been observed in some [Thomas et al., 1985]. Dural thickening at the craniocervical junction also can lead to cord compression neuropathy [Stevens et al., 1991]. Farther down the spine, the dural thickening (infiltration) may result in more peripheral neuropathy such as a neurogenic bladder as well as pain and parasthesias [Young et al., 1980]. Secondary syrinx of the cord (probably post traumatic) has been observed. Kyphosis, and even severe gibbus, is not unusual, also leading to neurologic symptomatology. Carpal tunnel syndrome can occur [Wraith et al., 1990].

CT and MRI changes. CT and MRI changes are quite similar in these disorders and appear to vary mostly in the severity of involvement [Lee et al., 1993; Murata et al., 1989; Taccone et al., 1993].

CT. Low attenuation areas occur in the brain white matter.

MRI. Delay in myelination may be present and high signal intensity on T2 with cystic areas scattered in many regions, which may be associated with ventriculomegaly. The anatomy of the involvement of the dura in the craniocervical region and lower spine is best delineated by this type of imaging. The same is apparent in MRI studies of the optic nerve.

This review of the neurologic findings in the skeletal dysplasias is meant to be helpful not only for the diagnosis of this large group of disorders, but also to be useful in the management of this diverse group of patients.

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